UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: May 9, 2013

SUBJECT: Tefluthrin: Review of Acute and Subchronic Neurotoxicity Studies

PC Code: 128912
Decision No.: 477888
Petition No.: NA
Risk Assessment Type: NA
TXR No.: 0056655
MRID No.: 49037002, 49037003

DP Barcode: D411269
Registration No.: NA
Regulatory Action: Follow-up
Case No.: NA
CAS No.: 79538-32-2
40 CFR: N/A

Ver.Apr. 2010

FROM: Chris Schlosser, Toxicologist
Risk Assessment Branch VI
Health Effects Division (7509P)

5/9/13

THROUGH: Felecia Fort, Branch Chief
Risk Assessment Branch VI
Health Effects Division (7509P)

Felecia Fort

TO: Molly Clayton, Chemical Review Manager
Risk Management and Implementation Branch 3
Pesticide Re-Evaluation Division (7508P)

I. CONCLUSIONS

The acute and subchronic neurotoxicity studies are acceptable and satisfy the guideline data requirements. In the acute neurotoxicity study, the no-observed adverse effect level (NOAEL) was 5 mg/kg/day, and the LOAEL was 10 mg/kg/day based on significantly decreased landing foot splay in both sexes, tremors (2/10, males only), and ataxia (m: 4/10, F: 2/10).

In the subchronic neurotoxicity study, the no-observed adverse effect level (NOAEL) in females was 150 ppm (13.6 mg/kg), and the LOAEL was 350 ppm (31.2 mg/kg/day) based on reduced body weights, increased landing footsplay, and clinical signs including: increased activity

(10/12), increased breathing rates (5/12), slight to moderate reduced splay reflex (11/12), and slight to moderate upward curvature of the spine (10/12). The NOAEL for male rats was 350 ppm (26.6 mg/kg), the highest dose tested.

II. ACTION REQUESTED

Review the acute and subchronic neurotoxicity studies to satisfy the data requirements for 870.6200 neurotoxicity screening battery.

III. BACKGROUND

HED was requested to review the acute and subchronic neurotoxicity studies to support the re-registration review of tefluthrin.

IV. RESULTS/DISCUSSION (or MRID Summary Table, etc.)

MRID Summary Table Example

Study Type	MRID	Comments
870.6200a Rat Acute Neurotoxicity Study	49037002	New DER
870.6200b Rat Subchronic (90 Day) Neurotoxicity Study	49037003	New DER

EPA Reviewer: Christopher Schlosser, M.F.S. **Signature:**
Risk Assessment Branch VI, Health Effects Division (7509P) **Date:** 5/9/13
EPA Secondary Reviewer: Deborah Smegal **Signature:**
Risk Assessment Branch VI, Health Effects Division (7509P) **Date:** 5/9/13

Template Version 09/11

TXR#: 0056655

DATA EVALUATION RECORD

STUDY TYPE: Acute Neurotoxicity - Rats OPPTS 870.6200a [§81-8]; OECD 424.

PC CODE: 128912 **DP BARCODE:** D411269

TEST MATERIAL (PURITY): Tefluthrin (92.4% a.i.)

SYNONYMS: (2,3,5,6-tetrafluoro-4-methylphenyl)methyl (1*R*,3*R*)-*rel*-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate

CITATION: Pinto, P.J. (2002) Tefluthrin – Acute Neurotoxicity Study in Rats. Syngenta Limited. Cheshire, UK. Report Number CTL/AR6767/REG/REPT, April 24, 2002. MRID 49037002. Unpublished

SPONSOR: Syngenta Crop Protection, LLC

EXECUTIVE SUMMARY:

In an acute neurotoxicity study (MRID 49037002), groups of (fasted) Wistar-derived rats (10/sex/dose) were given a single oral dose of (tefluthrin (92.4 a.i., batch/lot P25 (R151993: TSC 0295/05989) in corn oil at doses of 2.5, 5, or 10 mg/kg-bw and observed for 14 days. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 10 animals/sex/group one week prior to testing on day 1 (6-7 hours after administration, considered to be the time of peak effect), and on days 8 and 15. At study termination, 5 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, all were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

No treatment-related effects were identified on body weights, food consumption, motor activity, or histopathology.

Administration of 10 mg/kg of tefluthrin resulted in clear treatment-related neurotoxic effects at 6-7 hours post dosing and included decreased landing footsplay ($p<0.01$), tremors (males only), and ataxia (M: 4/10, F: 2/10). Additionally, increased breathing rates (2/10 males and 9/10 females) and increased fore-limb grip strength were identified in both sexes. Increased breathing rate persisted until study termination (day 15) in males, and study day 8 in females.

At 5 mg/kg, increased breathing rates were observed in both sexes and slight but significantly ($p<0.05$) decreased landing foot splay was reported in males only. Effects at this dose level were transient and showed rapid recovery. While a slightly decreased landing footsplay was identified

in male rats, it was in the absence of typical neurotoxic effects for Type I pyrethroids (aggression, hyper-excitability, fine tremor, prostration with coarse whole body tremor, and increased body temperature), and in the absence of other neurotoxic effects identified in the high dose group (ataxia and tremors). Therefore, the effects at this level were not considered to be of toxicological relevance.

Based on the results of this study, the LOAEL for neurotoxicity is 10 mg/kg-bw/day based on significantly decreased landing foot splay in both sexes, tremors (2/10, males only), and ataxia (M: 4/10, F: 2/10). The NOAEL for acute neurotoxicity of Tefluthrin is 5 mg/kg-bw/day.

This neurotoxicity study is classified as **acceptable/guideline** and satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424). In life dates and homogeneity analysis were not provided. However, this is not expected to cause a significant impact on study results.

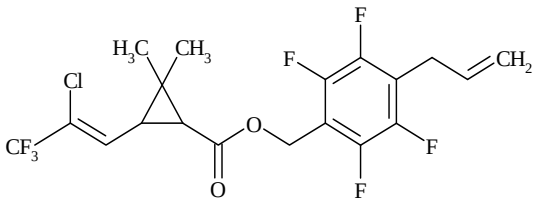
COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Tefluthrin

Description: Technical grade, off white glass-like solid
Lot/batch #: P25 (R151993: TSC 0295/05989)
Purity: 92.4% a.i.
CAS # of TGAI: 79538-32-2
Structure:



2. Vehicle and/or positive control: Corn oil

3. Test animals:

Species:	Rat	
Strain:	Wistar-derived Alpk:AP_f SD	
Age/weight at dosing:	42 days/184-240g (males), 129-182g (females)	
Source:	Rodent Breeding Unit, Alderley Park, Macclesfield, Cheshire, UK	
Housing:	5 per cage,	
Diet:	CT1 diet, supplied by Special Diet Services Limited, *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	22 ± 3°C
	Humidity:	30-70%
	Air changes:	At least 15/hr
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	At least 5 days prior to dosing	

B. STUDY DESIGN:

1. In life dates: In life dates were not provided. The study was initiated on 19th June 2000. The experimental phase began 4th July 2000 and was completed on 14th December 2000.

2. Animal assignment and treatment: Animals were assigned to the test groups noted in Table 1 using a computer-based randomization program. The animals were housed, sexed separately, in multiple rat racks with 5 rats per cage. Following an overnight fast, rats were given a single dose using a catheter and a disposable syringe of appropriate size then observed daily for 14 days and weighed on days 1, 2, 8 and 15. Dose levels were chosen based on results of previous studies. However, no citations were provided by study authors.

TABLE 1. Study design

Experimental parameter	Dose group (mg/kg-bw)			
	Control	2.5	5	10
Total number of animals/sex/group	10	10	10	10
Clinical Observations/Body Weights	10/sex	10/sex	10/sex	10/sex
Behavioral testing (FOB, Motor Activity)	10/sex	10/sex	10/sex	10/sex
Neuropathology	5/sex	-	-	5/sex

3. **Test Substance preparation and analysis**: For each dose, an appropriate amount of corn oil was added to provide one preparation of the required concentration. Rats were dosed at 10 ml/kg according to their individual body weight at time of dosing. The dose formulations were stored in a dark at room temperature. Concentration was verified for low and high dose levels over a period of 10 days.

Results:
Homogeneity analysis: N/A

Stability analysis: 100.0 to 105.1% of initial concentration following storage at room temperature (Table 2, Page 32 of study).

Concentration analysis: 98.0 to 108.0% of nominal concentration (Table 1, Page 31 of study).

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

4. **Statistics:** Bodyweights were considered by analysis of covariance on day 1, separately for males and females. Weekly food consumption, motor activity, time to tail-flick, landing foot splay and grip strengths were considered by analysis of variance, separately for males and females. Brain weights were considered by analysis of variance and by analysis of covariance on bodyweight. Analysis of variance and covariance were conducted using MIXED procedure. Least-squares means were calculated for each group using the LSMEAN option in SAS PROC MIXED. Differences from control were tested by comparing least squares mean values using a two-sided Student's t-test, based on the error mean square in the analysis.

C. METHODS / OBSERVATIONS:

1. **Mortality and clinical observations:** Animals were observed daily for mortality and morbidity. All rats were checked daily for clinical signs and significant changes were recorded.

2. **Body weight:** Animals were weighed at week -1, prior to dosing on day 1, at 6-7 hours after dosing on day 1 (estimated time of peak-effect, 6-7 hours following administration), and on days 2, 8, and 15.

3. **Food consumption:** Food consumption was recorded continuously throughout the study and calculated at weekly intervals, as a mean value (g/rat/day) for each cage.

4. **Cholinesterase determination:** Cholinesterase activity was not measured.

5. **Neurobehavioral assessment:**

   a. **Functional Observational Battery (FOB):** Detailed observations and quantitative assessments of landing foot splay, fore- and hindlimb grip strength, and sensory

perception were made in week -1, day 1 (time of peak effect, 6-7 hours following dosing), and on days 8 and 15. Evaluations were conducted by one observer who was "blind" with respect to treatment groups. Data was recorded by computer personnel not directly involved with the clinical observations. Criteria were scored as slight, moderate, or extreme, where appropriate.

The CHECKED (X) parameters were examined.

X	HOME CAGE OBSERVATIONS	X	HANDLING OBSERVATIONS	X	OPEN FIELD OBSERVATIONS
X	Posture*	X	Reactivity*	X	Mobility
	Biting	X	Lacrimation* / chromodacryorrhea		Rearing+
X	Convulsions*	X	Salivation*	X	Arousal/ general activity level*
X	Tremors*	X	Piloerection*	X	Convulsions*
X	Abnormal Movements*	X	Fur appearance	X	Tremors*
X	Palpebral closure*	X	Palpebral closure*	X	Abnormal movements*
X	Faeces consistency	X	Respiratory rate+	X	Urination / defecation*
		X	Red/crusty deposits*	X	Grooming
	SENSORY OBSERVATIONS	X	Mucous membranes /eye /skin colour	X	Gait abnormalities / posture*
X	Approach response+	X	Eye prominence*	X	Gait score*
X	Touch response+	X	Muscle tone*	X	Bizarre / stereotypic behaviour*
X	Startle response*			X	Backing
X	Pain response*		**PHYSIOLOGICAL OBSERVATIONS**		Time to first step
X	Pupil response*	X	Body weight*		
X	Eyeblink response	X	Body temperature+		**NEUROMUSCULAR OBSERVATIONS**
	Forelimb extension			X	Hindlimb extensor strength
	Hindlimb extension		**OTHER OBSERVATIONS**	X	Forelimb grip strength*
X	Air righting reflex+			X	Hindlimb grip strength*
	Olfactory orientation			X	Landing foot splay*
					Rotarod performance

*Required parameters; +Recommended parameters

b. <u>Locomotor activity</u>: Locomotor Activity was evaluated on week -1, day 1 (time of peak effect, 6-7 hours following administration), and on days 8 and 15. Activity was monitored using an automated recording device (large and small movements). Observation periods consisted of 10 scans of five minute duration.

6. <u>Sacrifice and pathology</u>: At termination (day 15), the designated groups 5/sex were deeply anaesthetized with I.P sodium pentobarbitone and skilled by perfusion fixation with modified Karnovsky's fixative, and submitted for neuropathology. Brain weights were recorded and the following tissues were analyzed: brain (7 levels), eye (with optic nerve and retina), spinal cord (including cervical and lumbar swellings), spinal nerve roots (dorsal and ventral root fibres), dorsal root ganglia, proximal sciatic nerve, proximal tibial nerve, distal tibial nerve and gastrocnemius muscle. 5 µm sections were cut and stained with hematoxylin and eosin, with the exception of transverse longitudinal section of the proximal sciatic nerve and the proximal and distal tibial nerve, these sections were cut semi-thin and stained with toluidine blue.

The CHECKED (X) tissues were evaluated.

X	CENTRAL NERVOUS SYSTEM	X	PERIPHERAL NERVOUS SYSTEM
	BRAIN		**SCIATIC NERVE**
X	Brain (7 levels)	X	Proximal sciatic nerve
			OTHER
			Sural Nerve
		X	Tibial Nerve
	SPINAL CORD		Peroneal Nerve
X	Cervical swelling	X	Lumbar dorsal root ganglion
X	Lumbar swelling	X	Lumbar dorsal root fibers
	Thoracic swelling	X	Lumbar ventral root fibers
	OTHER	X	Cervical dorsal root ganglion
	Gasserian Ganglion	X	Cervical dorsal root fibers
	Trigeminal nerves	X	Cervical ventral root fibers
X	Optic nerve		
X	Eyes		
X	Gastrocnemius muscle		

7. **Positive controls:** Five studies with MRID numbers 43013301 through 43013305 (performed in 1990-1992) and three studies with laboratory ID numbers: CTL/P/5632, CTL/WR0367/Regulatory/Report, and CLT/WR0365/Regulatory/Report (performed in 1997-2000) were performed by Syngenta to generate positive control data and validate the procedures and inter-observer reliability, to demonstrate the ability of the performing lab to conduct the FOB and to assess motor activity and neurotoxicity.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs:** Detailed clinical observations were conducted as part of the FOB assessment and are reported below.

2. **Mortality:** All animals survived until scheduled necropsy.

B. BODY WEIGHT AND BODY WEIGHT GAIN: No significant treatment-related effects were identified for either sex at any dose level.

TABLE 2. Body weight and body weight gain (g)

Observation (g ± s.d.)	Dose level (mg/kg bw)			
	Control	2.5	5	10
Body weight-males				
Day 1	208.4 ± 19	207.0 ± 10.1	203.4 ± 8.2	209.9 ± 12.4
Day 8	274.0 ± 21.6	271.6 ± 11.4	265.8 ± 8.1	272.1 ± 14.5
Day 15	322.1 ± 23.6	318.3 ± 10.3	311.1 ± 8.9	320.5 ± 17.3
Body weight-females				
Day 1	154.8 ± 10.3	155.2 ± 13.1	157.3 ± 13.7	151.6 ± 13.1
Day 8	184.6 ± 13.7	188.1 ± 15.2	189.0 ± 16.7	185.1 ± 15.3
Day 15	201.3 ± 16.4	202.4 ± 22.5	208.9 ± 17.7	201.6 ± 18.2

Data were extracted from study page 38
Values represent mean ± s.d.
n=10

C. FOOD CONSUMPTION: No significant treatment-related effects were identified on food consumption in either sex at any dose level.

D. CHOLINESTERASE ACTIVITIES: Cholinesterase activity was not evaluated.

E. NEUROBEHAVIORAL RESULTS:

1. **FOB findings:** In the 10 mg/kg group at 6-7 hours following administration (estimated time of peak effect), 4 males and 2 females were reported with slight ataxia, tremors were recorded in 2 males, and increased breathing rates were identified in 6 males and 9 females. Increased breathing rates persisted until study termination (day 15) in 2 males and study day 8 in 2 females. No further treatment-related findings were reported on study day 15. At 5 mg/kg, the only treatment-related effect identified was increased breathing rates in 4 males and 7 females, all animals recovered by study day 15. No treatment-related findings were identified at 2.5 mg/kg.

TABLE 3. Clinical observations

Observation	Dose Level (mg/kg bw/day)			
	Control	2.5	5	10
Males				
Ataxia	0/10	0/10	0/10	4/10
Increased breathing rate	0/10	0/10	4/10	6/10
Tremors	0/10	0/10	0/10	2/10
Females				
Ataxia	0/10	0/10	0/10	2/10
Increased breathing rate	0/10	0/10	7/10	9/10

Data were extracted from pages 34-36
Numbers represent the total number of observations/number of animals with at least one instance of the observation

Landing foot splay was significantly decreased on study day 1 (6-7 hours after dosing at time of peak effect) when compared to controls for both sexes in the 10 mg/kg group ($p<0.01$), and in males at 5 mg/kg ($p<0.05$). No effects on landing foot splay were identified beyond day 1. No statistically significant differences were identified on time to tail flick. Fore-limb grip strength was significantly increased in both sexes on day 15. No effects on hind-limb grip strength were observed in either sex at any time point during the study.

TABLE 7. Functional observation battery results

Observation	Dose level (mg/kg bw)			
	Control	2.5	5	10
Males				
Landing Foot Splay (mm)				
-Day -7	67.8 ± 9.2	62.7 ± 15.9	60.4 ± 14.5	56.9 ± 8.8
-Day 1	61.4 ± 10.7	52.0 ± 15.8	44.6 ± 5.3** (-27.4%)	46.6 ± 17.1* (-24.1%)
-Day 8	70.3 ± 15.3	72.0 ± 15.7	66.1 ± 15.0	67.2 ± 10.1
-Day 15	66.5 ± 10.1	67.6 ± 15.5	64.1 ± 12.6	68.6 ± 14.9
Forelimb Grip-Strength (g)				
-Day -7	370 ± 104	368 ± 68	343 ± 61	335 ± 71
-Day 1	575 ± 139	578 ± 142	630 ± 80	588 ± 71
-Day 8	768 ± 165	638 ± 143	773 ± 233	760 ± 183
-Day 15	800 ± 180	820 ± 174	943 ± 151	998 ± 175* (+24.6%)
Females				
Landing Foot Splay (mm)				
-Day -7	49.8 ± 13.6	50.6 ± 9.9	50.4 ± 7.7	48.0 ± 5.6
-Day 1	46.4 ± 11.0	44.3 ± 13.4	44.3 ± 13.4	35.7 ± 12.1* (-23.1%)
-Day 8	49.6 ±11.9	45.4 ± 9.5	45.4 ± 9.5	58.2 ± 13.7
-Day 15	50.5 ± 10.9	47.7 ± 14.5	47.7 ± 14.5	60.2 ± 17.2
Forelimb Grip-Strength (g)				
-Day -7	358 ± 87	388 ± 54	338 ± 48	365 ± 71
-Day 1	450 ± 62	410 ± 117	465 ± 72	523 ± 104
-Day 8	730 ± 134	663 ± 84	728 ±135	755 ± 89
-Day 15	653 ± 92	663 ± 116	755 ± 200	805 ±122* (+23.3%)

Data were extracted from pages 65 and 67 of the study
N=10
*=p<.05,** p<.01 compared with controls

2. **Motor activity:** No treatment-related effects were observed on motor activity on either sex at any time point in the study.

TABLE 8. Motor activity (total activity counts for session)

Test day	Dose level (mg/kg bw)			
	Control	2.5	5	10
Males				
Day -7	376.0 ± 207.3	348.2 ± 155.4	340.6 ± 133.8	349.2 ± 117.6
Day 1	460.4 ± 141.8	476.2 ± 137.6	495.0 ± 154.4	367.8 ±168.8
Day 8	427.2 ± 118.1	461.2 ± 174.2	419.6 ± 120.2	517.5 ± 123.3
Day 15	556.3 ± 121.9	512.4 ± 148.7	493.1 ± 121.2	598.2 ± 133.6
Females				
Day -7	578.6 ± 131.4	513.6 ± 155.5	583.9 ± 118.3	487.0 ± 100.2
Day 1	509.3 ± 169.9	605.5 ± 123.1	508.4 ± 168.5	424.7 ± 130.1
Day 8	407.3 ± 202.3	344.5 ± 107.2	497.4 ± 156.8	354.0 ± 118.1
Day 15	460.5 ± 183.2	515.0 ± 155.5	540.1 ± 173.1	404.4 ± 140.0

Data were extracted from pages 69 to 76 of the study
Values represent mean ±s.d.
N=10

F. SACRIFICE AND PATHOLOGY:

1. **Gross pathology:** No treatment-related gross observations were reported for either sex at any

dose level.

2. **Brain weight:** No treatment-related findings were reported on brain weights in either sex.

3. **Neuropathology:** No treatment-related microscopic findings were reported in nervous system tissues in either the control or 10 mg/kg groups.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

Single oral administration of 10 mg/kg tefluthrin resulted in clear treatment-related clinical signs (ataxia, increased breathing rate, and tremors), and decreased landing foot splay at 6-7 hours following dosing. Most changes showed rapid recovery with the exception of increased breathing rate in 2 male rats. Fore-limb grip strength was increased in both sexes on day 15 only.

At 5 mg/kg few effects were observed and showed full recovery by the end of the study. The observations at this dose level are considered to be of no toxicological significance. The NOAEL for this study is 5 mg/kg.

B. REVIEWER COMMENTS:

Administration of 10 mg/kg of tefluthrin resulted in clear treatment-related neurotoxic effects at 6-7 hours post dosing and included decreased landing footsplay ($p<0.01$), tremors (males only), and ataxia. Additionally, increased breathing rates and increased fore-limb grip strength were identified in both sexes. Increased breathing rate persisted until study termination (day 15) in males, and study day 8 in females.

At 5 mg/kg, increased breathing rates were observed in both sexes and slight but significantly ($p<0.05$) decreased landing foot splay was reported in males only. Effects at this dose-level were transient and showed rapid recovery. While a slightly decreased landing footsplay was identified in male rats, it was in the absence of typical of neurotoxic effects for Type I pyrethroids (aggression, hyper-excitability, fine tremor, prostration with coarse whole body tremor, and increased body temperature), and in the absence of other neurotoxic effects identified in the high dose group (ataxia and tremors). Therefore, the effects at this level were not considered to be of toxicological relevance.

Based on the results of this study, the LOAEL for neurotoxicity is 10 mg/kg-bw/day based on significantly decreased landing foot splay in both sexes, tremors (2/10, males only), and ataxia (M: 4/10, F: 2/10). The NOAEL for acute neurotoxicity of Tefluthrin is 5 mg/kg-bw/day.

This neurotoxicity study is classified as **acceptable/guideline** and satisfies the guideline requirement for an acute neurotoxicity study in rats (870.6200; OECD 424).

C. STUDY DEFICIENCIES:

In life dates and homogeneity analysis were not provided. However, this is not expected to cause a significant impact on study results.

EPA Reviewer: Christopher Schlosser, M.F.S. **Signature:**
Risk Assessment Branch VI, Health Effects Division (7509P) **Date:** 5/9/13
EPA Secondary Reviewer: Deborah Smegal **Signature:** Deborah C Smegal
Risk Assessment Branch VI, Health Effects Division (7509P) **Date:** 5/9/13

Template version 09/11

TXR#: 0056655

DATA EVALUATION RECORD

STUDY TYPE: Subchronic Neurotoxicity, OPPTS 870.6200b [§82-7] Oral Feed – Wistar Rats; (No OECD guideline).

PC CODE: 128912 **DP BARCODE:** D411269

TEST MATERIAL (PURITY): Tefluthrin (92.4% a.i.)

SYNONYMS: (2,3,5,6-tetrafluoro-4-methylphenyl)methyl (1*R*,3*R*)-*rel*-3-[(1*Z*)-2-chloro-3,3,3-trifluoro-1-propenyl]-2,2-dimethylcyclopropanecarboxylate

CITATION: Pinto, P.J. (2002) Tefluthrin – Subchronic Neurotoxicity Study in Rats. Syngenta Limited. Chesire, UK. Report Number CTL/PR1145/REG/REPT, April 29, 2002. MRID 49037003. Unpublished

SPONSOR: Syngenta Crop Protection, LLC

EXECUTIVE SUMMARY:

In a subchronic neurotoxicity study (MRID 49037003), tefluthrin (92.4 a.i., batch/lot P25 (R151993: TSC 0295/05989) was administered to 12 Wistar rats/sex/group at dose levels of 0, 50, 150, or 350 ppm (equivalent to 0, 3.8, 11.6, or 26.6 mg/kg-bw/day in males, and 0, 4.4, 13.4, or 31.2 mg/kg-bw/day in females) for 90 days. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed in 12 animals/sex/group on weeks -1, 2, 5, 9, and 14. Ophthalmoscopy was conducted all animals at study initiation and animals in the control and high-dose groups following treatment. At study termination, 5 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, all were subjected to histopathological evaluation of brain and peripheral nervous system tissues.

No treatment-related effects were observed on ophthalmoscopy, motor activity, time to tail flick, or hind-and forelimb grip strength in either sex.

Following administration of 0, 50, 150, or 350 ppm of tefluthrin in the diet, female Wistar rats appeared to be more sensitive to the effects. In the high-dose group, increased activity (10/12), ataxia (3/12), increased breathing rate (5/12), reduced splay reflex (slight: 7/12, moderate: 4/12), and upward curvature of the spine (slight: 9/12, moderate 1/12) was identified for female rats. The incidence and severity of increased breathing rate, reduced splay reflex, and upward curvature of the spine increased as the study progressed. Landing foot splay was statistically ($p<0.01$) increased in female rats at weeks 5, 9 and 14. Additionally, slight but significantly

($p<0.01$) decreased body weights (-7.1% at study termination) were identified from week 2 until study termination in females at the high dose. During neuropathological exam, one female rat at the high-dose was identified with focal cell loss in the granular layer of the cerebellum. As this is a rare lesion, and only occurred in one animal, the toxicological significance is unknown.

In male rats, slight but significantly ($p<0.05$) reduced body weights (-9.1% at study termination) were observed in the mid-dose group from week 7 to the end of the study. However, no dose-response was identified and male rats in the high-dose group were unaffected by treatment. Therefore, body weight effects were not considered to be treatment related. No effects on landing foot splay, motor activity, or neuropathology were identified for male rats. Clinical observations at week 14 included increased breathing rate in 1 animal and reduced splay reflex in 2 animals. Effects on clinical observations in male rats decreased in incidence and severity as the study progressed, and were not considered to be toxicologically significant.

Based on effects seen in females, a LOAEL of 350 ppm (equivalent to 31.2 mg/kg) was identified based on reduced body weights, increased landing foot splay, and clinical signs including increased activity (10/12), increased breathing rate (5/12), slight to moderate reduced splay reflex (11/12), and slight to moderate upward curvature of the spine (10/12). The NOAEL for female rats is 150 ppm (equivalent to 13.6 mg/kg).

A NOAEL of 350 ppm (26.6 mg/kg) was identified for male rats.

The study is classified **acceptable/guideline** and satisfies the guideline requirement for a subchronic neurotoxicity study in rats (870.6200b).

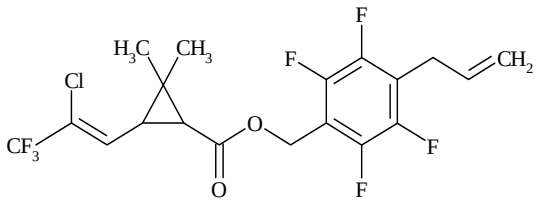
COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. Timing of the general clinical observations with respect to time after administration was not reported. However, this is not expected to impact the results of the study.

I. MATERIALS AND METHODS:

A. MATERIALS:

1. Test material: Tefluthrin

Description: Technical grade, off white glass-like solid
Lot/batch #: P25 (R151993: TSC 0295/05989)
Purity: 92.4% a.i.
CAS # of TGAI: 79538-32-2
Structure:



2. Vehicle and/or positive control: Corn oil

3. Test animals:

Species:	Rat	
Strain:	Wistar-derived Alpk:Ap_f SD	
Age/weight at dosing:	28-35 days/197-245g (males), 147-191g (females)	
Source:	Rodent Breeding Unit, Alderley Park, Macclesfield, Cheshire, UK	
Housing:	5 per cage initially, 4/cage after treatment assignment,	
Diet:	CT1 diet, supplied by Special Diet Services Limited, *ad libitum*	
Water:	Tap water, *ad libitum*	
Environmental conditions:	**Temperature:**	22 ± 3°C
	Humidity:	30-70%
	Air changes:	At least 15/hr
	Photoperiod:	12 hrs dark/12 hrs light
Acclimation period:	5 days prior to dosing	

B. STUDY DESIGN:

1. In life dates: Start: April 26, 2000; End: February 28, 2001

2. Animal assignment and treatment: Groups were arranged on two racks consisting of six single-sex randomized replicates. The sequence of groups in each replicate, noted in Table 1, was determined using computer-generated sequences of 1-4 (Latin square). Animals with adverse clinical signs, that failed the flick test, or that were at extremes of the weight range were discarded. The test substance was administered daily, in the diet, for at least 90 days. Dose levels were chosen based on the results of a previous study (Pinto 2002).

TABLE 1. Study design

Experimental parameter	Dose group (ppm)			
	Control	50	150	350
Total number of animals/sex/group				
Clinical Obs/Body Weights/Food Consumption	12/sex	12/sex	12/sex	12/sex
Ophthalmoscopy	12/sex	12/sex	12/sex	12/sex
Behavioral testing (FOB, Motor activity)	12/sex	12/sex	12/sex	12/sex
Neuropathology	5/sex	5/sex	5/sex	5/sex

3. Test Substance preparation and analysis:

The test diet was prepared in 30kg batches by mixing appropriate amounts of test substance (pre-dissolved with corn oil) with 950g of milled diet (CT1 diet supplied by Special Diets Services Limited, Stepfield, Witham, Essex, UK) and was stored at -20ºC. Homogeneity and stability were tested at room temperature and -20ºC. During the study, samples of treated food were analyzed over a period of 36 days at the high and low dose for stability and concentration.

Results

Homogeneity analysis: -10.6 to 7.8% deviation in mean concentration from three sampling points.

Stability analysis: 80.6 to 111.3% of initial concentration tested over 36 days at room temperature.

Concentration analysis: 86.6 to 109.6% of nominal concentration

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

4. Statistics: Bodyweights were considered by analysis of covariance on day 1, separately for males and females. Weekly food consumption, motor activity, time to tail-flick, landing foot splay and grip strengths were considered by analysis of variance, separately for males and females. Brain weights were considered by analysis of variance and by analysis of covariance on bodyweight. Analysis of variance and covariance were conducted using MIXED procedure. Least-squares means were calculated for each group using the LSMEAN option in SAS PROC MIXED. Differences from control were tested by comparing least squares mean values using a two-sided Student's t-test, based on the error mean square in the analysis.

C. METHODS / OBSERVATIONS:

1. Mortality and clinical observations: Animals were observed daily for mortality and morbidity. Detailed clinical observations were recorded prior to study initiation and on weeks 1, 3, 4, 6, 7, 8, 10, 11, 12, 13 and 14 at the same time that body weights were recorded. The time after dosing that clinical observations were conducted was not reported.

2. **Ophthalmoscopy:** Eyes from all rats were examined two to three weeks prior to study initiation. Eyes from control and high-dose rats were examined again during the week before termination.

3. **Body weight:** Animals were weighed one week prior to study initiation and then weekly for the duration of the study beginning at day 1 (prior to receiving first treatment), and on the same day of the week when practicable.

4. **Food consumption:** Food consumption was recorded continuously throughout the study and calculated at weekly intervals for each cage.

5. **Cholinesterase determination:** Cholinesterase activity was not determined.

6. **Neurobehavioral assessment:**

   a. **Functional observational battery (FOB):** Detailed clinical observations, landing foot splay, fore- and hind-limb grip strength, and sensory perception (tail-flick test) were conducted on weeks -1, 2, 5, 9, and 14. Time of observation was not reported. Observations were conducted by one person who was "blind" to treatment groups. Results were recorded on a computer system by personnel not directly involved with the observations. Degree of severity was recorded as slight, moderate or extreme.

The CHECKED (X) parameters were examined.

X	HOME CAGE OBSERVATIONS	X	HANDLING OBSERVATIONS	X	OPEN FIELD OBSERVATIONS
X	Posture*	X	Reactivity*	X	Mobility
	Biting	X	Lacrimation* / chromodacryorrhea		Rearing+
X	Convulsions*	X	Salivation*	X	Arousal/ gereral activity level*
X	Tremors*	X	Piloerection*	X	Convulsions*
X	Abnormal Movements*	X	Fur appearance	X	Tremors*
X	Palpebral closure*	X	Palpebral closure*	X	Abnormal movements*
X	Faeces consistency	X	Respiratory rate+	X	Urination / defecation*
		X	Red/crusty deposits*	X	Grooming
X	**SENSORY OBSERVATIONS**	X	Mucous membranes /eye /skin colour	X	Gait abnormalities / posture*
X	Approach response+	X	Eye prominence*	X	Gait score*
	Touch response+	X	Muscle tone*	X	Bizarre / stereotypic behaviour*
X	Startle response*			X	Backing
X	Pain response*				Time to first step
X	Pupil response*				
X	Eyeblink response	**X**	**PHYSIOLOGICAL OBSERVATIONS**	**X**	**NEUROMUSCULAR OBSERVATIONS**
X	Forelimb extension	X	Body weight*		Hindlimb extensor strength
X	Hindlimb extension	X	Body temperature+	X	Forelimb grip strength*
	Air righting reflex+			X	Hindlimb grip strength*
	Olfactory orientation			X	Landing foot splay*
		X	**OTHER OBSERVATIONS**		Rotarod performance

*Required parameters; +Recommended parameters

b. Locomotor activity: Locomotor Activity was evaluated on weeks -1, 2, 5, 9, and 14. Activity was monitored using an automated recording device (large and small movements). Observation periods consisted of 10 scans of five minute duration. Individual animals were returned to the same monitor at approximately the same time of day.

7. Sacrifice and pathology: At termination, the designated groups of 5/sex were deeply anaesthetized with I.P sodium pentobarbitone and killed by perfusion fixation with modified Karnovsky's fixative, and submitted for neuropathology. Brain weights were recorded and the following tissues were analyzed in the control and high dose groups: brain (7 levels), eye (with optic nerve and retina), spinal cord (including cervical and lumbar swellings), spinal nerve roots (dorsal and ventral root fibres), dorsal root ganglia, proximal sciatic nerve, proximal tibial nerve, distal tibial nerve and gastrocnemius muscle. 5 µm sections were cut and stained with hematoxylin and eosin, with the exception of transverse longitudinal section of the proximal sciatic nerve and the proximal and distal tibial nerve, these sections were cut semi-thin and stained with toluidine blue.

The CHECKED (X) tissues were evaluated.

X	CENTRAL NERVOUS SYSTEM	X	PERIPHERAL NERVOUS SYSTEM
	BRAIN		**SCIATIC NERVE**
X	Brain (7 levels)	X	Proximal sciatic nerve
			OTHER
			Sural Nerve
		X	Tibial Nerve
	SPINAL CORD		Peroneal Nerve
X	Cervical swelling	X	Lumbar dorsal root ganglion
X	Lumbar swelling	X	Lumbar dorsal root fibers
	Thoracic swelling	X	Lumbar ventral root fibers
	OTHER	X	Cervical dorsal root ganglion
	Gasserian Ganglion	X	Cervical dorsal root fibers
	Trigeminal nerves	X	Cervical ventral root fibers
X	Optic nerve		
X	Eyes		
X	Gastrocnemius muscle		

8. Positive controls: Five studies with MRID numbers 43013301 through 43013305 (performed in 1990-1992) and three studies with laboratory ID numbers: CTL/P/5632, CTL/WR0367/Regulatory/Report, and CLT/WR0365/Regulatory/Report (performed in 1997-2000) were performed by Syngenta to generate positive control data and validate the procedures and inter-observer reliability, to demonstrate the ability of the performing lab to conduct the FOB and to assess motor activity and neurotoxicity.

II. RESULTS:

A. OBSERVATIONS:

1. **Clinical signs:** General clinical signs included ataxia, upward curvature of the spine, increased breathing rate and increased response to sound in the high-dose group beginning at week 4. However, it should be noted that time of observation with respect to administration was not reported for the general clinical observations. Effects on the clinical condition of animals occurred at a higher frequency during the FOB observations. Therefore, clinical observations from the FOB evaluation, discussed below, will be considered.

2. **Ophthalmoscopy:** All animals had normal eyes prior to the study initiation. No effects were reported in either the control or high-dose group at week 13 prior to termination.

3. **Mortality:** All animals survived until study termination.

B. BODY WEIGHT AND BODY WEIGHT GAIN:

In the high-dose group, female rats had a significantly decreased body weight when compared to controls from week 2 until study termination. No effects were reported in the mid- and low-dose groups. In male rats, body weights were slightly lower than controls in all dose groups. However, a dose-response was not established and no statistical significance was identified for the high-dose group. Effects on body weight gain were not reported.

TABLE 2. Body weights (g ±s.d.)

Observation (g ± s.d.)	Dose level (ppm)			
	Control	50	150	350
Body weight-Males				
-Week 1	224.0 ± 11.7	219.9 ± 14.2	219.8 ± 10.7	217.8 ± 10.5
-Week 2	276.8 ± 13.3	270.7 ± 16.4	271.2 ± 12.1	267.3 ± 12.4
-Week 3	318.9 ± 14.1	308.2 ± 23.2	306.8 ± 15.3	304.8 ± 14.2
-Week 4	351.9 ± 16.1	337.6 ± 31.2	332.8 ± 19.3	335.2 ± 19.2
-Week 5	378.1 ± 20.6	359.7 ± 35.3	352.0 ± 23.2*	357.8 ± 23.2
-Week 6	404.1 ± 19.5	380.3 ± 37.6	372.5 ± 25.9*	377.3 ± 25.6
-Week 7	425.4 ± 20.0	400.8 ± 37.1	389.8 ± 28.4**	398.2 ± 30.6
-Week 8	446.1 ± 21.6	420.4 ± 41.4	406.7 ± 26.6**	414.0 ± 34.7
-Week 9	462.7 ± 21.9	439.1 ± 46.3	423.7 ± 29.1*	430.2 ± 38.5
-Week 10	482.3 ± 22.2	450.1 ± 48.9	441.1 ± 33.0*	448.8 ± 39.3
-Week 11	498.5 ± 23.7	462.3 ± 51.4	454.5 ± 34.6*	454.7 ± 41.5
-Week 12	509.4 ± 25.0	476.2 ± 52.9	467.2 ± 35.1*	476.3 ± 42.9
-Week 13	522.2 ± 25.0	484.4 ± 57.5	481.8 ± 34.3*	487.4 ± 46.6
-Week 14	532.2 ± 25.1	492.3 ± 54.7*	488.8 ± 37.5* (-8.2%)	494.7 ± 46.7
Body weight-Females				
-Week 1	162.2 ± 11.1	163.3 ± 5.5	160.5 ± 6.8	164.9 ± 11.0
-Week 2	184.8 ± 12.0	183.4 ± 11.1	181.3 ± 11.9	175.6 ± 10.6**
-Week 3	197.1 ± 19.3	197.1 ± 11.4	195.5 ± 12.0	184.9 ± 13.0**
-Week 4	211.2 ± 19.6	207.8 ± 15.0	209.8 ± 13.2	195.1 ± 13.1**
-Week 5	224.3 ± 20.2	220.9 ± 13.9	217.6 ± 11.1	202.8 ± 14.8**
-Week 6	236.0 ± 19.2	232.8 ± 14.4	231.0 ± 13.5	217.3 ± 11.9**
-Week 7	239.8 ± 23.1	238.8 ± 11.8	239.3 ± 19.8	220.8 ± 15.0**
-Week 8	244.3 ± 24.0	244.5 ± 16.0	244.3 ± 15.2	227.7 ± 10.9**
-Week 9	252.0 ± 24.1	254.6 ± 15.9	246.3 ± 11.0	231.6 ± 15.9**
-Week 10	260.1 ± 23.1	256.8 ± 16.9	255.6 ± 16.5	245.0 ± 14.6**
-Week 11	264.5 ± 23.4	260.0 ± 13.9	260.6 ± 15.5	249.0 ± 16.9**
-Week 12	267.9 ± 23.2	265.5 ± 19.8	268.0 ± 15.3	251.8 ± 17.3**
-Week 13	276.4 ± 23.5	272.6 ± 20.7	272.7 ± 12.6	258.9 ± 16.1**
-Week 14	278.1 ± 24.5	275.1 ± 18.0	274.5 ± 14.2	258.4 ± 15.7** (-7.1%)

Data were extracted from pages 57-60.

Values represent mean ± s.d.
n=12
*=p<.05, **=p<.01, when compared to control means.

C. FOOD CONSUMPTION:

A statistically significant decrease in food consumption was reported for male rats in all dose groups during the first 7 weeks of the study, and in female rats in the top dose group for the first 5 weeks of the study. Additionally, a significant decrease in food consumption was reported for mid-dose females for the first week of the study only.

TABLE 3. Food consumption (g/kg/day)

Week No.	Dose level (mg/kg bw/day)			
	Control	Low dose	Mid dose	High dose
Food Consumption-Males				
-Week 1	29.5 ± 0.7	28.1 ± 1.2*	28.7 ± 1.3	27.0 ± 0.8**
-Week 2	30.9 ± 0.8	29.3 ± 2.0	29.0 ± 1.4	28.4 ± 0.9*
-Week 3	30.7 ± 1.1	28.7 ± 1.7	29.3 ± 1.0	28.3 ± 0.5*
-Week 4	30.8 ± 1.7	28.5 ± 1.1	28.1 ± 0.4*	28.1 ± 0.4*
-Week 5	31.0 ± 1.2	28.9 ± 2.0	29.5 ± 1.5	28.3 ± 0.3
-Week 6	30.2 ± 0.6	28.2 ± 1.4*	27.5 ± 0.3**	28.5 ± 0.7
-Week 7	32.0 ± 0.7	29.5 ± 1.4*	29.0 ± 1.0**	29.2 ± 0.6**
-Week 8	32.7 ± 0.8	30.2 ± 2.4	30.3 ± 1.3	30.3 ± 0.6
-Week 9	30.4 ± 0.8	28.6 ± 2.4	28.6 ± 1.7	28.8 ± 1.2
-Week 10	30.9 ± 0.1	29.3 ± 1.8	28.7 ± 0.5*	29.2 ± 0.5
-Week 11	30.7 ± 0.4	29.3 ± 2.6	28.6 ± 0.9	29.3 ± 1.0
-Week 12	30.6 ± 0.4	28.4 ± 2.1	28.6 ± 0.6	29.3 ± 1.6
-Week 13	31.9 ± 0.9	29.8 ± 1.3	30.2 ± 0.5	30.3 ± 1.6
Food Consumption-Females				
-Week 1	21.7 ± 0.5	20.2 ± 2.1	18.4 ± 0.8*	18.1 ± 1.9*
-Week 2	20.0 ± 1.6	19.8 ± 1.3	19.4 ± 2.1	17.3 ± 0.8
-Week 3	21.4 ± 1.4	20.0 ± 1.6	20.5 ± 2.5	17.6 ± 0.3*
-Week 4	21.7 ± 0.9	20.5 ± 1.0	20.2 ± 0.6	18.3 ± 0.1**
-Week 5	21.4 ± 0.4	20.7 ± 0.9	20.4 ± 0.9	19.5 ± 0.4**
-Week 6	20.7 ± 0.3	20.5 ± 0.9	21.2 ± 1.4	19.1 ± 0.7
-Week 7	21.6 ± 0.4	21.7 ± 0.9	21.4 ± 1.0	20.4 ± 1.8
-Week 8	21.8 ± 0.8	22.4 ± 1.5	21.5 ± 0.2	21.0 ± 0.3
-Week 9	20.6 ± 0.5	19.6 ± 0.3	20.0 ± 0.9	20.3 ± 0.4
-Week 10	20.8 ± 1.1	19.8 ± 0.6*	20.2 ± 0.5	20.0 ± 0.4
-Week 11	21.1 ± 0.5	20.3 ± 1.1	21.1 ± 0.6	20.0 ± 0.3
-Week 12	21.2 ± 0.6	20.0 ± 0.9	20.9 ± 0.7	20.5 ± 0.6
-Week 13	21.7 ± 0.4	21.3 ± 0.3	21.7 ± 0.7	21.4 ± 0.7

Data were extracted from pages 61-64
Values represent mean ± s.d.
n=12
*=p<.05, **=p<.01, when compared to control means

D. CHOLINESTERASE ACTIVITIES: Cholinesterase activity was not measured.

E. NEUROBEHAVIORAL RESULTS:

1. FOB findings:

During week 14 of the FOB clinical assessment, increased activity (slight), ataxia (slight), increased breathing rate, reduced splay reflex (slight to moderate), and upward curvature of the spine (slight to moderate) was reported for female rats in the high-dose group. In male rats, one animal was identified with increased breathing rate and two animals with reduced splay reflex (slight) at the high-dose. In females, the incidence and severity of increased activity, upward curvature of the spine and reduced splay reflex, beginning at week 5, increased as the study progressed. Increased breathing rates and ataxia were identified in week 2 and week 5, respectively, and decreased in incidence as the study progressed for female rats only.

TABLE 4. Clinical observations at Week 14

Observation	Dose level (mg/kg bw/day)			
	Control	3.8-4.4 mg/kg	11.6-13.4 mg/kg	26.6-31.2 mg/kg
Males				
Increased Breathing Rate	0/12	0/12	0/12	1/12
Reduced Splay Reflex	0/12	0/12	0/12	2/12
Females				
Activity Increased	0/12	0/12	0/12	10/12
Ataxia	0/12	0/12	0/12	3/12
Increased Breathing Rate	0/12	0/12	1/12	5/12
Reduced Splay Reflex	2/12	1/12	1/12	7/12, slight 4/12, moderate
Upward Curvature of the Spine	0/12	0/12	1/12	9/12, slight 1/12 moderate

Data were extracted from pages 91-96
Numbers represent the total number of animals
n=12

No effects on landing foot splay were reported for male rats at any time point in the study at any dose level. A statistically significant ($p<0.01$) increase in landing foot splay was observed for females in the high-dose group at weeks 5, 9 and 14. A slight decrease in hindlimb grip strength was observed in males in the low- and high-dose during week 14 only. However, no dose-response was established. Additionally, hindlimb grip strength for all dose groups were within the ranges of historical controls. Forelimb grip strength was significantly lower in males and females at week 14 in the high-dose. However, values for individual rats were similar in control and 350 ppm groups with only one value outside concurrent control range. Therefore, changes on grip strength were not considered to be treatment-related.

TABLE 5. Functional observational battery results

Observation	Dose level (mg/kg bw/day)			
	Control	3.8-4.4 mg/kg	11.6-13.4 mg/kg	26.6-31.2 mg/kg
Males				
Landing Foot Splay				
Week -1	63.9 ± 11.2	64.3 ± 8.5	55.2 ± 10.1	60.4 ± 12.4
Week 2	86.3 ± 17.8	84.2 ± 14.1	83.3 ± 15.7	76.9 ± 18.5
Week 5	80.7 ± 20.1	75.5 ± 16.9	79.1 ± 17.1	75.8 ± 14.6
Week 9	71.0 ± 16.1	81.0 ± 18.8	72.9 ± 13.2	77.0 ± 20.6
Week 14	81.8 ± 13.6	74.8 ± 14.7	75.8 ± 12.7	73.0 ± 79.2
Females				
Landing Foot Splay				
Week -1	57.2 ± 10.1	52.8 ± 11.8	53.8 ± 7.2	56.4 ± 11.5
Week 2	65.1 ± 8.8	67.5 ± 17.6	67.1 ± 10.8	75.6 ± 16.3
Week 5	59.4 ± 11.4	61.6 ± 8.4	68.0 ± 16.6	83.9 ± 24.7**
Week 9	59.5 ± 16.7	61.1 ± 13.2	63.3 ± 11.4	98.4 ± 25.6**
Week 14	65.0 ± 16.2	61.1 ± 14.2	66.5 ± 15.0	85.8 ± 20.7** (+32%)

Data were extracted from pages 97 and 98
Values represent mean distance ± s.d. (mm)
N=12
*=p<.05,** p<.01 compared with controls

2. <u>Motor activity</u>: Mean locomotor activity was significantly reduced in high-dose females during week 9 observations. However, no significant differences were identified at week 14 or at any other time point in the study. Therefore, the difference at week 9 was not considered to be toxicologically relevant.

TABLE 6. Motor activity (total activity counts for session)

Test day	Dose level (mg/kg bw/day)			
	Control	3.8-4.4 mg/kg	11.6-13.4 mg/kg	26.6-31.2 mg/kg
Males				
Week -1	262.3 ± 100.6	340.2 ± 92.2	305.1 ± 115.7	321.1 ± 107.0
Week 2	405.3 ± 123.6	483.3 ± 124.4	466.1 ± 91.8	400.3 ± 102.3
Week 5	516.6 ± 147.9	581.3 ± 131.6	573.9 ± 143.6	505.9 ± 155.7
Week 9	452.1 ± 196.3	439.4 ± 127.0	498.8 ± 180.6	493.2 ± 141.5
Week 14	438.2 ± 165.8	504.7 ± 127.8	450.6 ± 173.8	467.1 ± 129.8
Females				
Week -1	432.6 ± 67.4	508.8 ± 145.7	440.1 ± 59.3	518.8 ± 175.9
Week 2	543.0 ± 244.5	558.6 ± 117.0	529.8 ± 182.4	495.8 ± 185.0
Week 5	721.6 ± 87.5	728.2 ± 114.1	692.3 ± 139.0	611.8 ± 181.9
Week 9	675.9 ± 51.3	682.8 ± 159.2	622.9 ± 131.1	544.1 ± 210.2*
Week 14	685.0 ± 55.6	676.0 ± 145.1	711.9 ± 81.7	624.0 ± 189.3

Data were extracted from pages 105, 111 and 112
Values represent mean <u>+</u>s.d.
n=12
*=p<.05,** p<.01 compared with controls

F. <u>SACRIFICE AND PATHOLOGY</u>:

1. <u>Gross pathology</u>: Gross pathology was not conducted.

2. Brain weight: No treatment-related findings were reported on brain weights in either sex.

3. Neuropathology:

One female rat in the high-dose group had focal cell loss in the granular layer of the cerebellum. As this is a rare lesion and not observed in controls the toxicological significance of this finding is uncertain. No remaining findings in the high-dose group were considered to be treatment-related and no treatment related lesions were identified in the low- or mid-dose groups for either sex.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS:

Oral administration of 350 ppm tefluthrin in the diet for 90 days resulted in clinical signs and increased landing foot splay in female rats. Neuropathological finding were limited to changes in brain pathology of 1 female at the high-dose group. Male animals were less affected and only displayed clinical signs in few animals at the high-dose.

Transient clinical signs in a small number of animals and decreased group mean food consumption in week 1 were identified in the mid-dose group and not considered to be toxicologically significant.

The NOAEL for toxicologically significant finding was considered to be 150 ppm.

B. REVIEWER COMMENTS:

Following administration of 0, 50, 150, or 350 ppm of tefluthrin in the diet, female Wistar rats appeared to be more sensitive to the effects. In the high-dose group, increased activity (10/12), ataxia (3/12), increased breathing rate (5/12), reduced splay reflex (slight: 7/12, moderate: 4/12), and upward curvature of the spine (slight: 9/12, moderate 1/12) was identified for female rats. The incidence and severity of increased breathing rate, reduced splay reflex, and upward curvature of the spine increased as the study progressed. Landing foot splay was statistically ($p<0.01$) increased in female rats at weeks 5, 9 and 14. Additionally, significantly ($p<0.01$) decreased body weights were identified from week 2 until study termination in females. During neuropathological exam, one female rat at the high-dose was identified with focal cell loss in the granular layer of the cerebellum. As this is a rare lesion, and only occurred in one animal, the toxicological significance is unknown.

In male rats, slight but significantly ($p<0.05$) reduced body weights (-9.1% at study termination) were observed in the mid-dose group from week 7 to the end of the study. However, no dose-response was identified and male rats in the high-dose group were unaffected by treatment. Therefore, body weight effects were not considered to be treatment related. No effects on landing foot splay, motor activity, or neuropathology were identified for male rats. Clinical observations at week 14 included increased breathing rate in 1 animal and reduced splay reflex in 2 animals. Effects on clinical observations in male rats decreased in incidence and severity as the study progressed, and were not considered to be

toxicologically significant.

Based on effects seen in females, a LOAEL of 350 ppm (equivalent to 31.2 mg/kg) was identified based on reduced body weights, increased landing foot splay, and clinical signs including increased activity (10/12), increased breathing rate (in 5/12), slight to moderate reduced splay reflex (11/12), and slight to moderate upward curvature of the spine (10/12). The NOAEL for female rats is 150 ppm (equivalent to 13.6 mg/kg).

A NOAEL of 350 ppm (26.6 mg/kg) was identified for male rats.

C. STUDY DEFICIENCIES: Recording of the general clinical observations with respect to time after administration was not reported. However, this is not expected to impact the results of the study.